(1) the existence of independent and distinct inventions (35 U.S.C. § 121); and

(2) that the search and examination of the entire application cannot be made without serious burden (M.P.E.P. § 803).

Applicants respectfully submit that the Examiner has not shown that the second requirement has been met with respect to any of the Groups and particularly with respect to Groups I and III above. Applicants contend that the searches required for claims drawn to methods of detecting predisposition to adverse pregnancy outcome and methods of treatment or selection of a therapeutic regimen would substantially overlap and would not require an undue search burden. Applicants note that a significant step in each of these claims is the detection of an IL-1 allele.

Furthermore, Applicants disagree with Examiner's statement that "[I]nvention III requires identifying a causative functional IL-1 mutation and selecting a therapeutic compensates for said mutation". In part, the present application demonstrates that various IL-1 alleles are associated with poor pregnancy outcomes. This result alone demonstrates that there exists at least one mutation in linkage disequilibrium with the above IL-1 alleles that contributes to an increased risk of poor outcome. The existence of at least one functional mutation may be inferred without identifying that mutation. Similarly the ability of a therapeutic to compensate for at least one functional mutation may be determined without identifying the mutation. In certain embodiments, all of this may be achieved by using one or more pregnancy outcome-associated allele as an indicator of the presence of one or more functional mutations.

Therefore, it is Applicant's position that the restriction requirement is in error and that the Examiner has not shown that a serious burden would be required to examine all the claims, and in particular Applicant urges that the search required for Groups I and III is not substantially greater than the search required for either Group I or Group III alone.

The Examiner further requires the election of one of the nucleic acids represented in SEQ ID NOS: 1-18 for the purposes of Groups I-IV.

Applicants strenuously object to this restriction requirement, in part because it would force Applicants to prosecute claims that are not operative with respect to many preferred embodiments. SEQ ID NOS: 1-18 are oligonucleotides that hybridize to certain IL-1 or TNFA nucleic acids. These oligonucleotides may be used to detect various alleles by various methods (see, for example, claim 3). One method for detecting alleles involves polymerase chain reaction (PCR) -based amplification. PCR typically requires two oligonucleotides in order to work. The sequence election requirement would limit Applicant to claims drawn to only one oligonucleotide, thereby making it impossible for Applicants to claim methods wherein PCR might be used! Such a restriction in the claims would permit others to use preferred embodiments of Applicant's methods with impunity. This problem appears to arise from the Examiner's misapplication of the principle that different nucleic acids are different inventions. While the principle may reflect current case law with respect to composition of matter type claims, Applicants assert that it is not intended to be applied to method claims, and particularly to method claims where the inventiveness does not necessarily derive from the nucleic acid sequences alone. SEQ ID NOS: 1-18 are merely 18 examples of the multitude of tools available to one of skill in the art to accomplish the methods claimed in the present application, albeit tools that, if claimed individually as compositions of matter, might represent distinct inventions. If Examiner's reasoning in making this sequence election requirement for method claims is correct, Examiner might just as well restrict the claims to methods using a particular brand of centrifuge or methods using a particular shape of test tube. If the Examiner insists on maintaining the sequence election requirement, then Applicants elect SEQ ID NO:1, but solely to achieve responsiveness.

In conclusion, Applicants request reconsideration and withdrawal of this Restriction Requirement.

CLEAN SET OF CLAIMS AS AMENDED AND AS PENDING UPON ENTRY OF THIS RESPONSE:

1. A method for determining whether a subject is predisposed to having an adverse pregnancy outcome, said method comprising the steps of:

a) obtaining a nucleic acid sample from the subject; and

b) detecting an IL-1A (+4845) allele 2 or an IL-1 (-511) allele 2 or an allele in linkage disequilibrium with an IL-1A (+4845) allele 2 or an IL-1 (-511) allele 2 in a sample, wherein detection of the IL-1A (+4845) allele 2 or the IL-1 (-511) allele 2 or the allele in linkage disequilibrium with the IL-1A (+4845) allele 2 or the IL-1 (-511) allele 2 indicates that the fetus is predisposed to an adverse pregnancy outcome.

2. The method of claim 1, wherein the adverse pregnancy outcome is low birth weight.

3. The method of claim 1, wherein said detecting step is selected from the group consisting of

allele specific oligonucleotide hybridization; size analysis; sequencing; hybridization; 5' nuclease digestion; single-stranded conformation polymorphism; allele specific hybridization; primer specific extension; and oligonucleotide ligation assay.

4. The method of claim 1, wherein prior to the detection step, the nucleic acid sample is subject to an amplification step.

5. The method of claim 4, wherein said amplification step employs a primer selected from the group consisting of any of SEQ ID No: 1 through SEQ ID No:18.

6. The method of claim 3, wherein said size analysis is preceded by a restriction enzyme digestion.

7. A method of claim 6, wherein said restriction enzyme digestion uses a restriction enzyme selected from the group consisting of: Nco I, Alu I and Msp I.

8. A method of identifying an allele associated with an low birth weight, said method comprising identifying an allele, which is in linkage disequilibrium with IL-1A (+4845) allele 2 and/or an IL-1 (-511) allele 2.

17. **(Amended)** A method for selecting an appropriate therapeutic to administer to a pregnant woman predisposed to having a low birth weight baby, comprising the steps of: determining the IL-1 genotype of the individual to identify whether the subject contains an low birth weight (LBW) associated allele and selecting a therapeutic that compensates for an LBW causative functional mutation that is in linkage disequilibrium with the polymorphism.

18. The method of claim 17, wherein the low birth weight baby is pre-term or pre-mature.

19. The method of claim 17, wherein said genotyping is selected from the group consisting of:

allele specific oligonucleotide hybridization; size analysis; sequencing; hybridization; 5' nuclease digestion; single-stranded conformation polymorphism; allele specific hybridization; primer specific extension; and oligonucleotide ligation assay.

20. The method of claim 17, wherein prior to the genotyping, the nucleic acid sample is subjected to an amplification step.

21. The method of claim 20, wherein said amplification step employs a primer selected from the group consisting of any of SEQ ID No:1 through SEQ ID No:18.

22. The method of claim 19, wherein said size analysis is preceded by a restriction enzyme digestion.

23. The method of claim 22, wherein said restriction enzyme digestion uses a restriction enzyme selected from the group consisting of: Nco I, Alu I and Msp I.

24. The method of claim 17, wherein the therapeutic is selected from the group consisting of: a corticosteroid, antimetabolite, cytotoxic drug, colchicine or an anticytokine.

25. **(Amended)** The method of claim 17, wherein the therapeutic is selected from the group consisting of: a modulator of an IL-1 activity and a modulator of a TNF activity.

26. **(Amended)** The method of claim 25, wherein the modulator of an IL-1 activity is IL-1α.

27. **(Amended)** The method of claim 25, wherein the modulator of an IL-1 activity is IL-1β.

28. **(Amended)** The method of claim 25, wherein the modulator of an IL-1 activity is IL-1Ra.

29. The method of claim 25, wherein the therapeutic is a protein, peptide, peptidomimetic, small molecule or a nucleic acid.

30. The method of claim 25, wherein the modulator is an agonist.

31. The method of claim 25, wherein the modulator is an antagonist.

32. The method of claim 17, wherein the LBW associated allele is IL-1A (+4845) allele 2 or an IL-1 (-511) allele 2 or an allele that is in linkage disequilibrium with IL-1A (+4845) allele 2 or an IL-1 (-511) allele 2.

42. **(Amended)** A method for treating a subject predisposed to having a low birth weight baby (LBW) comprising the steps of: determining the IL-1 genotype of the individual to identify the presence of an LBW associated allele; and administering to the subject a

therapeutic that compensates for an LBW causative mutation that is in linkage disequilibrium with the polymorphism.

43. The method of claim 42, wherein the low birth weight baby is pre-term or premature.

44. The method of claim 42, wherein said genotyping is selected from the group consisting of:

allele specific oligonucleotide hybridization; size analysis; sequencing; hybridization; 5' nuclease digestion; single-stranded conformation polymorphism; allele specific hybridization; primer specific extension; and oligonucleotide ligation assay.

45. The method of claim 42, wherein prior to the genotyping, the nucleic acid sample is subjected to an amplification step.

46. The method of claim 45, wherein said amplification step employs a primer selected from the group consisting of any of SEQ ID No:1 through SEQ ID No:18.

47. The method of claim 44, wherein said size analysis is preceded by a restriction enzyme digestion.

48. The method of claim 47, wherein said restriction enzyme digestion uses a restriction enzyme selected from the group consisting of: Nco I, Alu I and Msp I.

49. The method of claim 42, wherein the therapeutic is selected from the group consisting of: a corticosteroid, antimetabolite, cytotoxic drug, colchicine or an anticytokine.

50. **(Amended)** The method of claim 42, wherein the therapeutic is selected from the group consisting of: a modulator of an IL-1 activity and a modulator of a TNF activity.

51. **(Amended)** The method of claim 50, wherein the modulator of an IL-1 activity is IL-1α.

52. **(Amended)** The method of claim 50, wherein the modulator of an IL-1 activity is IL-1β.

53. **(Amended)** The method of claim 50, wherein the modulator of an IL-1 activity is IL-1Ra.

54. The method of claim 50, wherein the therapeutic is a protein, peptide, peptidomimetic, small molecule or a nucleic acid.

55. The method of claim 50, wherein the modulator is an agonist.

56. The method of claim 50, wherein the modulator is an antagonist.

57. The method of claim 42, wherein the LBW associated allele is IL-1A (+4845) allele 2 or an IL-1 (-511) allele 2 or an allele that is in linkage disequilibrium with IL-1A (+4845) allele 2 or an IL-1 (-511) allele 2.

80. A method of determining increased susceptibility to an adverse pregnancy outcome, said method comprising:

(a) detecting an IL-1 allele 2 of a marker in a nucleic acid from a specimen collected from a fetus;

wherein detecting said IL-1 allele 2 marker indicates the individual's increased susceptibility to an adverse pregnancy outcome.

81. The method of claim 80, wherein said adverse pregnancy outcome is a premature preterm-low birth weight delivery.

5' TCCTGGTCTGCAGGTAA 3' (SEQ ID No: 16)

5' AAGCTTGTTCTACCACCTGAACTAGGC 3' (SEQ ID No: 17)

5' TTACATATGAGCCTTCCATG 3' (SEQ ID No: 18)

CONCLUSION:

If there are any fees in connection with the filing of this Response to Restriction Requirment, please charge the fees to our **Deposit Account No. 06-1448.** If a fee is required for an extension of time under 37 C.F.R. §1.136, such an extension is requested and the fee should also be charged to our Deposit Account. Please note that Applicants claim Small Entity Status, and any fees should be charged accordingly.

Respectfully submitted,

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